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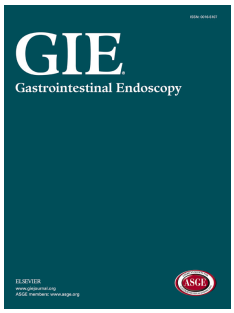

Time latencies of *Helicobacter pylori* eradication after peptic ulcer and risk of recurrent ulcer, ulcer adverse events, and gastric cancer: a population-based cohort study

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Conflicts of interest: None.

Abstract

Background: *Helicobacter pylori* (*H pylori*) is associated with peptic ulcer disease and gastric cancer.

Aim: To test how various lengths of delays in *H pylori* eradication therapy influence the risk of recurrent peptic ulcer, ulcer adverse events and gastric cancer.

Methods: This population-based nationwide Swedish cohort study included 29,032 patients receiving *H pylori* eradication therapy after peptic ulcer disease in 2005-2013. Pre-defined time intervals between date of peptic ulcer diagnosis and date of eradication therapy were analysed in relation to study outcomes. Cox regression provided hazard ratios (HRs) and 95% confidence intervals (95% CIs), adjusted for age, sex, comorbidity, history of ulcer disease, use of ulcerogenic drugs, and use of proton pump inhibitors (PPIs).

Results: Compared to eradication therapy within 7 days of peptic ulcer diagnosis, eradication therapy within 8 to 30, 31 to 60, 61 to 365, and >365 days corresponded with HRs of recurrent ulcer of 1·17 (95% CI, 1·08-1·25), 2·37 (95%,CI, 2·16-2·59), 2·96 (95%,CI, 2·76-3·16), and 3·55 (95% CI, 3·33-3·79), respectively. The corresponding HRs for complicated ulcer were 1·55 (95% CI, 1·35-1·78), 3·19 (95% CI, 2·69-3·78), 4·00 (95% CI, 3·51-4·55), and 6·14, 95% CI, 5·47-6·89), respectively. For gastric cancer, the corresponding HRs were 0·85 (95% CI, 0·32-2·23), 1·31 (95% CI, 0·31-5·54), 3·64 (95% CI, 1·55-8·56), and 4·71 (95% CI, 2·36-9·38), respectively.

Conclusions: Delays in *H pylori* eradication therapy after peptic ulcer diagnosis time-dependently increase the risk of recurrent ulcer, and even more so for complicated ulcer, starting from delays of 8 to 30 days.

Introduction

Infection with *Helicobacter pylori (H pylori),* a bacterium that frequently colonizes the human stomach, is a strong and causal risk factor for peptic ulcer disease and gastric cancer [1-3]. Worldwide, 95% of duodenal and 70% of gastric ulcers are associated with *H pylori* [4]. In Sweden, the prevalence of *H pylori* among adults is approximately 30%, which is lower than in most countries [5]. A peptic ulcer diagnosis with a positive test for *H pylori* is the main indication for *H pylori* eradication therapy, which usually includes treatment with 2 antibiotics and a proton pump inhibitor (PPI). However, not all patients hospitalized for peptic ulcer disease have their *H pylori* infection confirmed whilst hospitalized, and subsequently do not always receive *H pylori* eradication therapy shortly after the peptic ulcer diagnosis. Instead, these patients are initially only prescribed a PPI, which does not eradicate *H pylori*. Delays in eradication therapy can be due to several reasons, including forgetfulness, false negative tests for *H pylori* [6], lack of biopsy samples (eg, in situations with emergency bleeding or perforation) or *H pylori* resistance (an increasing problem worldwide) [7]. In fact, an earlier review from the Swedish Council on Health Technology Assessment has shown that only 43% of patients hospitalized for peptic ulcer bleeding in Sweden did not receive *H pylori* eradication therapy within 90 days of diagnosis [8]. The consequences of delays in *H pylori* eradication therapy regarding risk of recurrent ulcer or gastric cancer are unclear. The scarce literature examining these issues has indicated that delays >120 days and >365 days might increase the risk of recurrent ulcer [9] and gastric cancer, respectively [10].

We aimed to test the hypothesis that various lengths of delays in *H pylori* eradication therapy increase the risk of recurrent peptic ulcer disease, complicated peptic ulcer disease, and gastric cancer in a large and population-based cohort study.

Materials and methods

Design

This nationwide and population-based cohort study included all adults (≥18 years) diagnosed with peptic ulcer and receiving *H pylori* eradication therapy in Sweden during the study period July 1, 2005 to December 31, 2013. The study exposure was various predefined time latencies between peptic ulcer diagnosis and *H pylori* eradication therapy and the outcomes were recurrent peptic ulcer, peptic ulcer complicated by perforation or bleeding, and gastric cancer. The study was approved by the Regional Ethical Review Board in Stockholm (number 2014/1291-31/4).

Cohort members

All members of the study cohort had peptic ulcer disease and *H pylori* eradication therapy during the study period. Patients with gastric cancer diagnosis before or within 1 year of the index hospitalization for peptic ulcer were excluded, as were patients with Zollinger-Ellison syndrome (a gastrin-secreting pancreatic tumor).

Data on peptic ulcer disease and *H pylori* eradication therapy were retrieved from the Swedish Patient Registry and the Swedish Prescribed Drug Registry, respectively. The Patient Registry held data on all diagnoses recorded at hospitalizations and out-clinic specialist care in Sweden during the entire study period. The diagnosis codes K25-K27 in the 10th version of the International Classification of Diseases (ICD-10) were used to define peptic ulcer disease. The completeness of main diagnoses is approximately 95% in this registry [11]. Diagnoses of gastric and duodenal ulcers are supposed to be confirmed by endoscopy according to Swedish guidelines, and indeed the Swedish Cancer Registry, which records 98% of all diagnosed gastric cancer cases, has 100% completeness of histological verification of these tumors [12]. The Prescribed Drug Registry records all prescribed and dispensed drugs in Sweden (approximately 9.5 million inhabitants) since July 1, 2005 [13]. This registry contains information on names of prescribed drug substances according to the anatomical therapeutic chemical classification (ATC) [13]. *H pylori* eradication therapy was defined according to ATC-codes representing the standard recommendations for eradication therapy in Sweden: A02BC (PPI) and any two of J01CA04 (amoxicillin) or J01FA09 (clarithromycin) or J01XD (metronidazole), including the only combination package for eradication therapy available in Sweden, ie, A02BD06 (Nexium HP). Included were also combinations that are recommended whenever primary eradication therapy fails: PPIs + metronidazole + doxycycline (J01AA02) + bismuth (A02BX05) or PPIs + amoxicillin +

levofloxacin (J01MA12). All antibiotic prescriptions needed to be dispensed at the same date to fulfil the inclusion criteria. For PPIs, a window was allowed from 60 days before to 5 days after the antibiotic prescription because many people already have PPIs prescribed and for continuous use the standard package is for 100 days of use.

Exposure definition

The exposure was defined as the time interval between the date of peptic ulcer diagnosis and the date of eradication therapy of *H pylori*, which was categorized into 5 predefined groups: ≤7 days, 8 to 30 days, 31 to 60 days, 61 to 365 days, and >365 days. The choice of time intervals was pre-defined and based on clinical relevance. The index episode of peptic ulcer was the first one occurring during the study period. For patients with several treatments to accomplish *H pylor*i eradication, the latest treatment during the study period was counted as the eradication therapy occasion.

Outcome definition

There were 3 outcomes: (1) recurrence of peptic ulcer occurring >30 days after the index peptic ulcer diagnosis (a peptic ulcer diagnosis within 30 days from the index peptic ulcer was defined as the same peptic ulcer), (2) peptic ulcer complicated by bleeding or perforation >30 days after the index diagnosis, and (3) gastric cancer occurring >1 year after the index peptic ulcer diagnosis. Recurrent ulcer was defined by the ICD-

10 codes K25-K27 as recorded in the Patient Registry. Ulcers complicated with perforation or bleeding were defined by the ICD-10 codes K25.0-2, K25.4-6, K26.0-2, K26.4-6, K27.0-2, and K27.4-6 in the Patient Registry. The Swedish Cancer Registry was used to assess gastric cancer with the ICD-10 code C16. The Swedish Cancer Registry has 98% complete registration of type and date of gastric cancer diagnoses in Sweden [12].

Censoring

Censoring of follow-up for mortality or migration was enabled by collecting data from the Swedish Registry of the Total Population, which provided complete information on dates of death and emigration for all cohort members with a maximum delay of 14 days [14].

Confounders

Selected as potential confounding factors were age, sex, comorbidity, history of ulcer disease, use of ulcerogenic drugs, and use of PPIs. Data on age, sex, comorbidities and history of ulcer disease were retrieved from the Patient Registry. Comorbidity was defined using the most updated version of the Charlson Comorbidity Index, which has been developed and well validated to enhance international transferability using register data for weighting comorbidity and provide comorbidity scores for each individual [15]. Information about all diagnoses included in the Charlson Comorbidity Index was retrieved from the Patient Registry. Ulcer history was defined by an ulcer diagnosis (ICD-7 codes 540-541, ICD-8 codes 531-533, ICD-9 codes 531-533, and ICD-10 codes K25-K27) recorded >30 days before the index ulcer diagnosis in the Patient Registry.

Use of ulcerogenic drugs was defined as ≥2 prescriptions of any of the following medications after the date of the index ulcer: aspirin (ATC-code B01AC and N02BA01), other nonsteroidal anti-inflammatory drugs (NSAIDs) (ATC-codes M01AB, M01AC, M01AE and M01AH) or clopidogrel (ATC-code B01AC04). This definition was chosen to include individuals with more or less regular use of the drug under study, not individuals who used the drug occasionally. Use of PPIs was defined as ≥2 prescriptions of PPIs (ATC-code A02BC) between the index ulcer date and recurrent ulcer or gastric cancer or the end of the study, in addition to the PPIs that were prescribed during the *H pylori* eradication therapy. Data on use of ulcerogenic drugs and PPIs were retrieved from the Prescribed Drug Registry.

Statistical analysis

Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). *H pylori* eradication therapy within 7 days after peptic ulcer diagnosis was the reference category in all analyses. Multivariable models were created to adjust for age (continuous variable), sex (male or female), comorbidity (Charlson Comorbidity Index score 0, 1, or ≥2) [15], and ulcer history (yes or no). In the analysis examining recurrence of peptic ulcer, we further adjusted for use of ulcerogenic drugs (yes or no) and PPIs (yes or no). Follow-up continued until death, emigration, date of recurrent peptic ulcer (with or without adverse event), date of gastric cancer, or end of the study period (December 31, 2013), whichever occurred first. To evaluate potential interactions, stratified analyses were conducted for each of the potential confounders included in the multivariable model. All analyses were performed using the statistical software IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp).

Results

Patients

In total, 29,032 patients with peptic ulcer who had *H pylor*i eradication therapy were included in the final study cohort. During the mean follow-up time of 75 months (2268 days), 7629 patients had recurrent peptic ulcer, 2050 had peptic ulcer adverse events, and 50 patients developed gastric cancer. Characteristics of the study participants are shown in Table 1. More than half of the patients were men (57.0%). A slight majority of the patients (65.8%) received *H pylori* eradication therapy ≤7 days after the peptic ulcer diagnosis. Comparing the patients in the five different time latency categories, there were only minor differences in the crude frequencies of age, sex, and comorbidity, whereas the use of ulcerogenic drugs and PPIs (outside the eradication therapy period) differed more. Tobacco-related disorders were evenly distributed across categories of lengths of delays in *H pylori* eradication therapy. Alcohol-related disorders were similar for the first categories of delays, but were slightly more common in the last 2 categories of delay. Contacts with healthcare (for any indication) were slightly higher in the last two delay categories (Table 1).

Risk of recurrent peptic ulcer

The risk of recurrent peptic ulcer increased for each longer time latency category between the primary peptic ulcer diagnosis and *H pylori* eradication therapy (Table 2). Compared to patients with *H pylori* eradication therapy within 7 days of diagnosis, patients receiving eradication therapy 8-30 days after diagnosis had a 17% increased risk of recurrent ulcer (HR 1.17; 95% CI, 1.08-1.25). The HRs increased for each longer latency category, and the HR was over 3-fold in the patients treated with *H pylori* eradication therapy >365 days after ulcer diagnosis (HR 3.55; 95% CI, 3.33-3.79).

Stratification for age showed that patients below the mean age had a slightly higher risk of recurrent ulcer than patients above the mean age (Table 3). Results were similar for men and women. The risk of recurrent ulcer with delayed *H pylori* eradication therapy was higher among patients with no comorbidities than those who had comorbid conditions. Users of ulcerogenic drugs had an increasing risk over time compared with non-users, in those with >60 days latency interval. Patients with PPI use outside the eradication therapy period also had a more pronounced increase in risk with latencies >60 days than patients not taking such medication (Table 3). In analyses stratified for inpatient or outpatient care at index diagnosis, the results remained similar in both groups (Supplementary Table 1). Stratification for duodenal or gastric ulcer showed a more pronounced increase in risk for duodenal ulcers, but the dose-response association remained, regardless of ulcer location (Table 3).

Risk of peptic ulcer with perforation or bleeding

Even stronger associations were found between time delays of *H pylori* eradication therapy and risk of peptic ulcer complicated by perforation or bleeding (Table 2). Compared with patients receiving *H pylori* eradication therapy within 7 days after peptic ulcer diagnosis, those with *H pylori* eradication therapy between 8 and 30 days after a peptic ulcer diagnosis had a 55% increased risk of complicated ulcer (HR 1.55; 95% CI, 1.35-1.78). The HRs increased for each longer latency category to an over 6-fold risk in patients with eradication therapy delayed by >365 days (HR 6.14; 95% CI, 5.47-6.89). Stratified analyses showed higher HRs in older age groups for latency intervals >60 days, whereas no major differences were found between the sexes (Table 3). The risk of ulcer adverse events with long delay in *H pylori* eradication therapy was higher among patients with no comorbidities than those who had comorbid conditions. Among patients using ulcerogenic drugs, as well as among patients with PPI-use outside the eradication therapy period, the risk of ulcer adverse events was higher with delayed eradication therapy compared with patients not using these drugs (Table 3).

Risk of gastric cancer

The risk of gastric cancer was increased in latency intervals of >60 days between peptic ulcer and eradication therapy (Table 2). Compared with patients receiving *H pylori* eradication therapy within 7 days after peptic ulcer diagnosis, patients receiving eradication therapy 61 to 365 days after a peptic ulcer diagnosis had an over 3-fold increased HR of gastric cancer (HR 3.64; 95% CI, 1.55-8.56) and the HR was nearly 5-fold

increased with >365 days delay (HR 4.71; 95% CI, 2.36-9.38). Robust stratification analyses were not possible for gastric cancer due to the limited number of events. Thus, gastric cancer was not included in Table 3.

Discussion

This study indicates strong and time-dependent associations between increased lengths of delay in *H pylori* eradication therapy after peptic ulcer and risks of peptic ulcer recurrence, ulcer adverse events and possibly gastric cancer. The risk of recurrent ulcer and ulcer adverse events increased already after an 8- to 30-day delay, whereas the risk of gastric cancer was increased after a delay of 61 to 365 days.

Methodological strengths include the population-based design with an unselected cohort of virtually all eligible patients in Sweden, accuracy and completeness of data on exposures and outcomes, adjustment of several potential confounders, completeness of follow-up, and the large sample size allowing analyses of several time latency categories. As in any observational study, a limitation is the potential influence of unknown confounding. Direct data on the lifestyle factors tobacco smoking and alcohol overconsumption were for example not available. However, the adjustment for comorbidities included conditions related to these exposures, ie, chronic obstructive lung disease and liver cirrhosis, which should reduce any confounding by these factors. Another issue might be misclassification of relevant medications due to that some medications obtained over-the-counter could not be taken in to account. However, this should not influence the results much because antibiotics are not sold over the counter in Sweden, and PPIs and ulcerogenic drugs are much more expensive to buy over the counter. Another

source of error is the lack of data on how *H pylori* infection was determined in each case. However, any such misclassification should be at random and therefore only dilute associations and not explain the positive associations of this study. The time intervals of delay were chosen based on earlier research. We cannot exclude that this can lead to some overestimation of early recurrences in patients with gastric ulcer at index diagnosis because these patients usually undergo a repeat endoscopy within 6 to 8 weeks. However, when results are stratified for ulcer location, the increased recurrence risk is more pronounced for duodenal ulcers than for gastric ulcers, making it unlikely that a possible slight overestimation would much affect the results. Also, any potential misclassification due to this would be nondifferential, ie, be similar in patients having had delayed eradication therapy or not and thus rather dilute than explain the association. The length of follow-up for recurrent ulcer and ulcer adverse events was sufficient, but for gastric cancer a longer follow-up would have been preferable and stratified analyses were not possible. Nevertheless, the HRs of gastric cancer in the main analyses were statistically significantly increased for the longer time delay categories in this study. Yet, the results for gastric cancer should be interpreted cautiously. The MALT lymphomas, a special group of gastric tumors that are well documented to be associated with *H pylori* infection, were too few to be analyzed in this material.

The association between time delays in *H pylori* eradication therapy and risk of recurrent ulcer has, to the best of our knowledge, only been examined in 2 previous studies. A retrospective cohort study from Taiwan compared “early” (≤120 days) and “late” (>120 days) eradication therapy among 1,900 patients with peptic ulcer hospitalization, and found an increased risk of recurrent ulcer after late eradication therapy

(HR 1.52; 95% CI, 1.13-2.04) [9]. The same research group also examined the effect of the 120 days latency within a group of patients with end-stage renal disease and found similar results, with a lower risk of recurrence in the early eradication therapy group (HR 0.76; 95% CI, 0.64-0.91) [16]. The present study, with a 15-fold larger number of patients supports the results of these previous studies. Importantly, this study also adds the dimension of a time-dependent pattern with risks of recurrent ulcer associated with both shorter and longer delays in *H pylori* eradication therapy.

The finding of an increased risk of complicated ulcer disease associated with delays in *H pylori* eradication therapy is new. It is possible that *H pylori* infection interacts with endogenous factors in the patients that increase the risk of recurrence of adverse events. A certain genotype of the plasminogen activator inhibitor type 1 that suppresses fibrinolysis is, for example, associated with recurrence of peptic ulcer bleeding [17].

The hypothesis that delayed eradication therapy increases the risk of gastric cancer was proposed in a Taiwanese study, showing that among 80,255 patients with a >365 days delay of eradication therapy the risk of gastric cancer was 36% increased compared to the general population, whereas patients receiving *H pylori* eradication therapy within 365 days experienced no increase [10]. These findings are partly consistent with the results of the present study, although this study shows that even shorter delays (61-365 days) could increase the risk of gastric cancer. It has earlier been suggested that long-term use of PPI can increase the risk of gastric cancer, which is supported by a recent large cohort study

from Hong Kong [18]. In our study, PPI use outside the eradication period was considered at confounding factor and was adjusted for in all models. *H pylori* infection contributes to the development of peptic ulcer and gastric cancer by inducing chronic inflammation and atrophy of the gastric mucosa, and cancer development is further promoted by genetic changes in the gastric epithelial cells. *H pylori* infection is suggested to be a promoter, rather than an initiator in the causal chain that leads to cancer of the stomach [19]. A randomized trial from China found that in patients without precancerous gastric lesions, the risk of gastric cancer was decreased after *H pylori* eradication therapy [20]. A recent meta-analysis from our group found a protective effect of *H pylor*i eradication therapy on gastric cancer risk [21]. It is possible that the series of events after *H pylori* infection leading to a peptic ulcer represents an increased inflammatory and cell damaging activity that can ultimately promote cancer development. If this process is inhibited by eradication therapy at an early stage, both recurrent ulcer and cancer may be prevented. This stresses the need for early detection and eradication of *H pylori* infection among peptic ulcer patients, a notion supported by the findings of the present study.

This study is the first to show a consistent time-dependent association between increased time latencies in *H pylori* eradication therapy and the risk of recurrent ulcer, ulcer adverse events, as well a possible association with gastric cancer. These findings, together with the available previous literature and the biological plausibility, argue in favor of causality, but more large-scale studies are needed to confirm these findings in other populations. Yet, assuming that the findings of the present study are correct, calculations of the population attributable risk show that

23% of recurrent ulcers, 33% of complicated ulcers, and 30% of gastric cancers could be avoided if all patients received eradication therapy within 30 days from their initial peptic ulcer diagnosis.

It is notable that delays of *H pylori* eradication therapy are not uncommon, particularly in light of the well-functioning and all-encompassing healthcare system in Sweden, which is accessible for all residents almost without any cost and without private insurance. The reasons for delayed eradication therapy are not clear, but in the absence of strong contra-indications for such eradication therapy, factors that might contribute include forgetfulness, false negative tests for *H pylori,* lack of biopsy samples, or *H pylori* resistance. The strengths of the associations between delays in eradication therapy resulting in increased risks of ulcer recurrence, ulcer adverse events and also gastric cancer indicate a need to make efforts to reduce such delays. The Swedish Prescribed Drug Registry was initiated in 2005, and earlier data on eradication therapy are unfortunately not available. However, the prevalence of antibiotic resistance is very low in Sweden. A systematic review from 2010 showed that Sweden had the lowest prevalence of *H pylori* clarithromycin resistance of all investigated countries, only 1.5% [22] As false negative tests of *H pylori* are common in emergency situations [6], it is advisable to re-test patients with a negative *H pylori* test in the emergency setting. The re-testing should be performed in close proximity to the primary ulcer diagnosis, with PPI-medication withdrawn 2 weeks before testing, to avoid false negative results due to transformation into coccoid form of *H pylori* caused by PPI. Advocating a more

liberal attitude toward eradication therapy in patients with peptic ulcer, even in the absence of proven *H pylori* infection, might even be justified.

In conclusion, this large and population-based cohort study shows that the length of delay in *H pylori* eradication therapy after peptic ulcer diagnosis is strongly and time-dependently associated with an increased risk of recurrent ulcer and even more so the risk of complicated peptic ulcer. Longer delays in eradication therapy can possibly also increase the risk of gastric cancer. These findings emphasize the relevance of implementing safe clinical strategies to expedite *H pylori* eradication associated with peptic ulcer disease.

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Table 1. Characteristics of the study cohort members, consisting of patients with peptic ulcer diagnosis, treated with Helicobacter pylori eradication in Sweden in 2005-2013, presented as number (%).

		Time latency categories in *Helicobacter pylori* eradication after peptic ulcer Number of patients (%)					
		Total cohort	**≤ 7 days**	**8-30 days**	**31-60 days**	**61-365 days**	**>365 days**
Total number		29 032 (100%)	19 089 (65.8%)	4 141 (14.3%)	1 407 (4.8%)	2 193 (7.6%)	2 202 (7.6%)
Number of ulcer events		7629	3798	936	535	1130	1230
Number of complicated ulcer events		2050	826	276	158	326	464
Number of gastric cancer events		50	23	5	2	7	13
Mean age (years)		64.6	63.9	70.0	67.0	63.4	59.9
Sex	**Male**	16 549 (57.0%)	11 226 (58.8%)	2199 (53.1%)	736 (52.3%)	1 219 (55.6%)	1169 (53.1%)
	Female	12 483 (43.0%)	7863 (41.2%)	1942 (46.9%)	671 (47.7%)	974 (44.4%)	1 033 (46.9%)
Charlson comorbidity score	**0**	10474 (36.1%)	7454 (39.0%)	1070 (25.8%)	439 (31.2%)	721 (32.9%)	790 (35.9%)
	1	6905 (23.8%)	4456 (23.3%)	1013 (24.5%)	350 (24.9%)	529 (24.1%)	557 (25.3%)
	>1	11653 (40.1%)	7179 (37.6%)	2058 (49.7%)	618 (43.9%)	943 (43.0%)	855 (38.8%)
Use of ulcerogenic drugs	**Yes**	10 871 (37.4%)	7 251 (38.0%)	1 496 (36.1%)	482 (34.3%)	688 (31.4%)	954 (43.3%)
	No	18 161 (62.6%)	11 838 (62.0%)	2 645 (63.9%)	925 (65.7%)	1 505 (68.6%)	1 248 (56.7%)

Use of proton pump inhibitors outside eradication period	**Yes**	12 895 (44.4%)	8 059 (42.2%)	2 066 (49.9%)	574 (40.8%)	934 (42.6%)	1 262 (57.3%)
	No	16 137 (55.6%)	11 030 (57.8%)	2 075 (50.1%)	833 (59.2%)	1 259 (57.4%)	940 (42.7%)
Tobacco related diseases	**Yes**	2 603 (9%)	1 560 (8.2%)	449 (10.8%)	137 (9.7%)	238 (10.9%)	219 (9.9%)
	No	26 429 (91%)	17 529 (91.8%)	3 692 (89.2%)	1 270 (90.3%)	1 955 (89.1%)	1 983 (90.1%)
Alcohol related diseases	**Yes**	2 422 (8.3%)	1 425 (7.5%)	358 (8.6%)	112 (8.0%)	234 (10.7%)	293 (13.3%)
	No	26 610 (91.7%)	17 664 (92.5%)	3 783 (91.4%)	1 295 (92.0%)	1 959 (89.3%)	1 909 (86.7%)
Mean number of health care visits during the study period (standard deviation)		32.1 (40.8)	29.7 (36.9)	33.2 (44.4)	31.8 (48.9)	38.8 (48.5)	44.5 (48.4)

Table 2. Latency intervals between peptic ulcer and Helicobacter pylori eradication therapy in relation to risk of recurrent peptic ulcer, ulcer complicated by bleeding or perforation and gastric cancer, expressed as hazard ratios (HR) and confidence intervals (CI)

	Recurrent ulcer			Complicated ulcer			Gastric cancer		
Latency interval	**Number of cases (person years)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**	**Number of cases (person years)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**	**Number of cases (person years)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
≤ 7 days	3 798 (2 035)	1.00 (reference)		826 (509)	1.00 (reference)		23 (46)	1.00 (reference)	
8-30 days	936 (452)	1.21 (1.13-1.30)	1.17 (1.08-1.25)	276 (128)	1.66 (1.44-1.90)	1.55 (1.35-1.78)	5 (5)	1.15 (0.44-3.03)	0.85 (0.32-2.23)
31-60 days	535 (136)	2.30 (2.10-2.52)	2.37 (2.16-2.59)	158 (41)	3.13 (2.64-3.71)	3.19 (2.69-3.78)	2 (0)	1.47 (0.35-6.22)	1.31 (0.31-5.54)
61-365 days	1 130 (466)	3.04 (2.84-3.25)	2.96 (2.76-3.16)	326 (139)	4.08 (3.59-4.64)	4.00 (3.51-4.55)	7 (8)	3.77 (1.62-8.81)	3.64 (1.55-8.56)
>365 days	1 230 (2 188)	2.75 (2.58-2.93)	3.55 (3.33-3.79)	464 (786)	4.77 (4.25-5.34)	6.14 (5.47-6.89)	13 (29)	4.72 (2.39-9.32)	4.71 (2.36-9.38)
p for trend		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001

* Adjusted for age, sex, comorbidity, history of ulcer disease, use of ulcerogenic drugs and use of proton pump inhibitors.

Table 3. Stratified analyses of latency interval between peptic ulcer and Helicobacter eradication in relation to risk of recurrent peptic ulcer and complicated ulcer, expressed as hazard ratios (HR) and confidence intervals (CI). Analyses stratified for age, sex, comorbidity, use of ulcerogenic drugs, use of proton pump inhibitor (PPI) and ulcer location.

Stratification variable		Time latency categories in Helicobacter pylori eradication after peptic ulcer				
		Risk of recurrent ulcer				
		≤ 7 days	8-30 days	31-60 days	61-365 days	>365 days
		HR* (95% CI)	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)
Age	**< Mean**	1.00 (reference)	1.29 (1.14-1.47)	2.44 (2.09-2.85)	3.32 (2.99-3.68)	4.07 (3.71-4.47)
	≥ Mean	1.00 (reference)	1.14 (1.04-1.24)	2.28 (2.04-2.55)	2.70 (2.47-2.95)	2.98 (2.72-3.27)
Sex	**Male**	1.00 (reference)	1.16 (1.05-1.28)	2.19 (1.93-2.50)	2.90 (2.64-3.17)	3.62 (3.32-3.96)
	Female	1.00 (reference)	1.18 (1.06-1.31)	2.55 (2.25-2.90)	3.02 (2.74-3.34)	3.44 (3.13-3.80)
Charleson Comorbidity Index	**0**	1.00 (reference)	1.30 (1.12-1.50)	2.50 (2.11-2.98)	3.55 (3.14-4.02)	4.69 (4.17-5.27)
	1	1.00 (reference)	1.20 (1.04-1.39)	2.69 (2.27-3.20)	3.00 (2.61-3.45)	3.54 (3.10-4.03)
	>1	1.00 (reference)	1.10 (1.00-1.22)	2.10 (1.83-2.40)	2.70 (2.41-2.93)	2.84 (2.57-3.13)
Use of ulcerogenic	**Yes**	1.00 (reference)	1.11 (0.91-1.36)	1.10 (0.79-1.53)	4.69 (3.95-5.56)	6.60 (5.78-7.53)

drugs	**No**	1.00 (reference)	1.17 (1.08-1.27)	2.57 (2.34-2.83)	2.65 (2.46-2.85)	2.93 (2.72-3.17)
Use of PPI besides eradication period	**Yes**	1.00 (reference)	1.28 (1.08-1.51)	1.20 (0.89-1.61)	3.86 (3.30-4.52)	5.74 (5.09-6.49)
	No	1.00 (reference)	1.16 (1.07-1.25)	2.59 (2.36-2.85)	2.62 (2.43-2.82)	2.75 (2.54-2.99)
Gastric ulcer		1.00 (reference)	1.01 (0.91-1.11)	1.65 (1.47-1.85)	2.18 (1.99-2.39)	2.41 (2.18-2.67)
Duodenal ulcer		1.00 (reference)	1.24 (1.11-1.37)	3.34 (2.89-3.86)	3.76 (3.41-4.15)	4.65 (4.27-5.06)
		Risk of recurrent ulcer adverse events				
		HR* (95% CI)	**HR* (95% CI)**	**HR* (95% CI)**	**HR* (95% CI)**	**HR* (95% CI)**
Age	**< Mean**	1.00 (reference)	1.58 (1.23-2.04)	2.98 (2.19-4.07)	4.67 (3.81-5.71)	6.82 (5.73-8.10)
	≥ Mean	1.00 (reference)	1.55 (1.32-1.83)	3.23 (2.63-3.97)	3.61 (3.05-4.28)	5.41 (4.62-6.34)
Sex	**Male**	1.00 (reference)	1.56 (1.30-1.88)	3.04 (2.40-3.84)	3.99 (3.37-4.73)	6.60 (5.69-7.66)
	Female	1.00 (reference)	1.54 (1.25-1.90)	3.36 (2.62-4.31)	4.02 (3.29-4.92)	5.53 (4.61-6.65)
Charleson Comorbidity Index	**0**	1.00 (reference)	1.77 (1.32-2.40)	3.72 (2.65-5.21)	5.04 (3.89-6.52)	9.55 (7.72-11.88)
	1	1.00 (reference)	1.70 (1.30-2.22)	3.19 (2.27-4.48)	3.97 (3.05-5.18)	5.77 (4.56-7.31)
	>1	1.00 (reference)	1.39 (1.15-1.68)	2.88 (2.26-3.68)	3.60 (3.00-4.31)	4.72 (3.99-5.59)
Use of ulcerogenic	**Yes**	1.00 (reference)	1.02 (0.68-1.54)	0.81 (0.38-1.73)	5.83 (4.26-7.97)	10.02 (7.92-12.68)

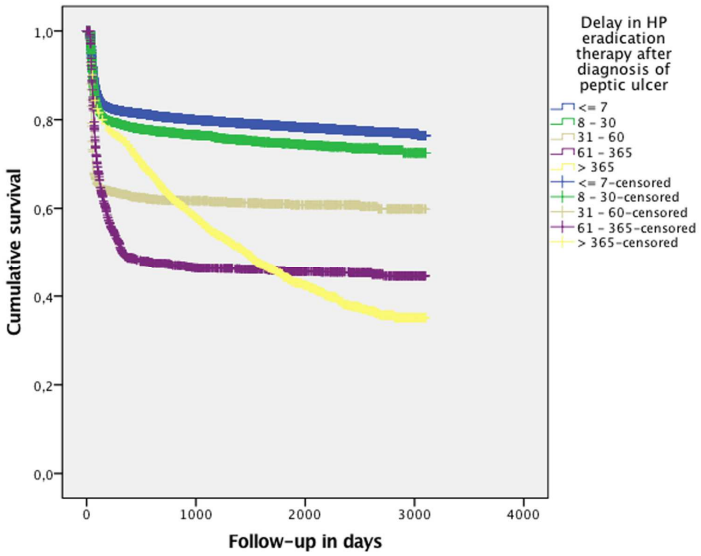
drugs	**No**	1.00 (reference)	1.64 (1.42-1.90)	3.67 (3.08-4.38)	3.59 (3.12-4.14)	5.19 (4.53-5.94)
Use of PPI besides eradication period	**Yes**	1.00 (reference)	1.43 (1.04-1.95)	1.63 (0.99-2.67)	4.47 (3.34-5.97)	8.43 (6.78-10.48)
	No	1.00 (reference)	1.60 (1.37-1.86)	3.57 (2.98-4.28)	3.62 (3.14-4.19)	5.02 (4.36-5.79)
Gastric ulcer		1.00 (reference)	1.16 (0.94-1.45)	2.21 (1.73-2.81)	2.87 (2.36-3.49)	4.19 (3.43-5.11)
Duodenal ulcer		1.00 (reference)	1.90 (1.59-2.27)	5.01 (3.94-6.37)	5.38 (4.52-6.40)	7.69 (6.66-8.87)

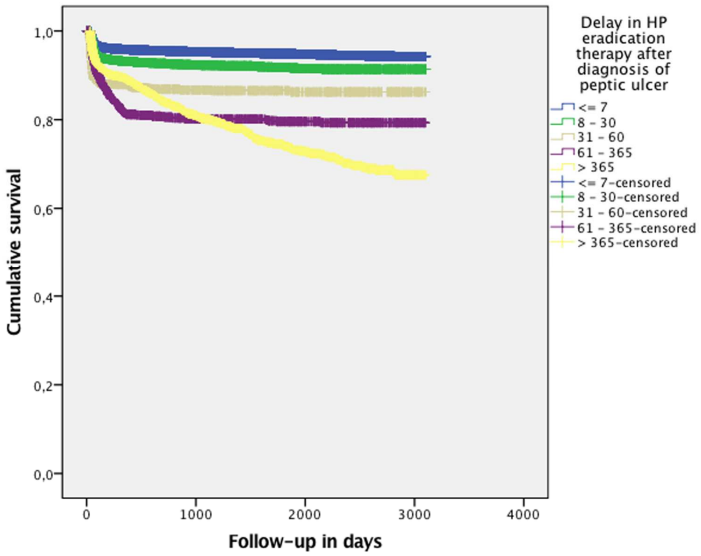
* Adjusted for age, sex, comorbidity index, use of ulcerogenic drugs and use of PPI, when applicable

Supplementary table. Latency intervals between peptic ulcer and *Helicobacter pylori* eradication in relation to risk of recurrent peptic ulcer and ulcer complicated by bleeding or perforation, expressed as hazard ratios (HR) and confidence intervals (CI). Stratified for inpatient or outpatient care at index diagnosis.

	Inpatient care at index diagnosis	
	Recurrent ulcer	**Complicated ulcer**
Latency interval	**Adjusted HR* (95% CI)**	**Adjusted HR* (95% CI)**
≤7 days	1.00 (reference)	1.00 (reference)
8-30 days	1.20 (1.10-1.31)	1.50 (1.30-1.74)
31-60 days	2.46 (2.19-2.76)	3.21 (2.66-3.88)
61-365 days	2.86 (2.62-3.12)	3.59 (3.10-4.15)
>365 days	3.60 (3.30-3.93)	5.75 (5.02-6.58)
	Outpatient care at index diagnosis	
	Recurrent ulcer	**Complicated ulcer**
Latency interval	**Adjusted HR* (95% CI)**	**Adjusted HR* (95% CI)**
≤7 days	1.00 (reference)	1.00 (reference)
8-30 days	1.09 (0.95-1.24)	0.82 (0.51-1.32)
31-60 days	2.22 (1.92-2.57)	2.89 (1.93-4.35)
61-365 days	3.04 (2.73-3.39)	4.84 (3.62-6.46)
>365 days	3.52 (3.19-3.88)	8.05 (6.40-10.12)

* Adjusted for age, sex, comorbidity, history of ulcer disease, use of ulcerogenic drugs and use of proton pump inhibitors.





Acronyms in order of appearance

H. pylori	-	Helicobacter pylori
HR	-	Hazard ratio
CI	-	Confidence interval
PPI	-	Proton pump inhibitor
ICD	-	International Classification of Diseases
ATC	-	Anatomical therapeutic chemical classification
NSAID	-	Non-steroidal anti-inflammatory drug